****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0265
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	02/21 09:25
USAGE T	00'42
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** February 21, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached questions that need to be addressed in order to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

1. The combination treatment portion of study 25 demonstrates that the addition of steroids to PS-341 can improve a patient's response. What data exist regarding the minimum steroid dose that produces an additive effect with PS-341?

2. The response rate (CR or CR(IF+)) for patients with light chain disease is 28.6% or 8/28 compared with the response > rate (CR or CR(IF+)) for patients who do not have light chain disease is 6.3% or 11/174. The differences in response rate seem puzzling especially when patients with light chain disease are thought to have a more aggressive disease which can be quite resistant to therapy. Please comment.

3. Please provide a data listing for the 19 patients who are CR or CR (IF+) of the duration of response to prior therapy. Please give the patient ID, the prior therapy, and the duration of response to prior therapy.

per Tonya Lewis on 21FEB03: We won't have duration of response data. We have TTP on prior by Thomas.

4. Please discuss whether the peripheral/sensory neuropathy seen with PS-341 resolves when PS-341 is discontinued.

5. Please discuss whether the musculoskeletal/connective tissue toxicity seen with PS-341 resolves when PS-341 is discontinued.

6. Please discuss treatment strategies for neuropathy including dose reduction, other medications, and supportive care.

Regarding your E-NDA database:

1. Datasets - some of the datasets use different patient ID numbers - for example the "conmed" dataset uses "MPID;" the "IRC_PID" uses "CNOPATNO," and "Demo" uses "PNO."

2. Is there a dataset which provides cross referencing for these patient ID numbers across datasets? If not, please provide one.

3. Does the NDA contain the patient graphs of type, duration and response to prior therapy as contained in your Dec 2 background package?

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 10, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to you Expanded Access Protocol——for Velcade (bortezomib) for Injection submitted to the Agency January 16, 2003.

Please review the following comments:

The proposed endpoint of response vs no change would provide relatively little information concerning the efficacy of the addition of dexamethasone to velcade. We suggest you consider adding complete response rates as a primary endpoint and survival as a secondary endpoint, and perform a formal statistical analysis.

In addition, Dr Pazdur requests that you delay initiation of your Velcade expanded access study until we can discuss administrative aspects of the program and the potential effects on your registration trials. We would prefer to schedule a discussion of Velcade access issues in the context of your total clinical development program at the time of your NDA presentation.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

MESSAGE CONFIRMATION

02/10/03 15:22
ID=FDA-DODP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/10	00'34"	617 551 3742	CALLING	01	OK	0000

02/10/03 15:21 FDA-DODP → 916175513742 NO.015 P01

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 10, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 5, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Tanya,

The Division of Oncology Drug Products is piloting a new process for orienting the review team to new NDAs. We invite you give a 1-hour presentation of your NDA to the Division. This may be followed by 30 minutes of questions and discussion. The purpose of this presentation is to provide the review team with a summary of the NDA and your perspective on why the drug should be approved.

This presentation is scheduled for February 24, 2003 at 400-530 PM EST and you may wish to be available after the presentation to answer questions from the review team regarding the NDA format or to assist in locating information within the NDA.

In addition we would like to have an extensive discussion of your plans to fulfill the demonstration of clinical benefit which would include a description of the study, how many studies, and estimated times of completion.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

MESSAGE CONFIRMATION

02/05/03 15:19
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/05	00'35"	617 551 3742	CALLING	01	OK	0000

02/05/03 15:18 FDA-DODP → 916175513742 NO.031 D01

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 5, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 3, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Tanya,

Regarding the presentation for Velcade.

We would like you to present a one hour presentation similar to what you would give at ODAC, covering critical CMC issues, summaries of critical pharmacology/toxicology issues, and pharmacokinetics, and extensive discussion of clinical trials.

We would also like you to present the Clinical Pharmacology studies submitted in the NDA, results and labeling impact and what Clin-Pharm studies are ongoing for future submission and a brief analysis and comparison of all the observed clinical and non-clinical neurotoxicity.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

MESSAGE CONFIRMATION

02/03/03 12:07
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/03	00'33"	617 551 3742	CALLING	01	OK	0000

02/03/03 12:06 FDA-DODP → 916175513742 NO.001 P01

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 3, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 3	**Date:** January 31, 2003
Re: NDA 21-602, VELCADE (1)	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Tanya,

Please submit the attached information to the Division of Scientific Investigations at the following address:

Khin Mating U, M.D.
Medical Officer
Division of Scientific Investigations (HFD-45)
7520 Standish Place, Room 125
Rockville, MD 20855
Phone: (301) 827-7383
Fax: (301) 827-5290

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

Part I: **Please submit the following data:**

- NDA number, commercial and generic name of the drug product, chemical classification (whether new molecular entity or not), pharmacologic class (e.g., antiarrhythmic agent), and the indication(s) sought
- Sponsor's submission date, expected filing meeting date and expected user fee goal date
- Mention whether the review is standard or priority
- A copy of Volume 1.1 of NDA
- Name and phone number of sponsor's contact person for the NDA
- General list of reportable AEs
- List of pivotal studies considered "critical" for this NDA. For each **pivotal study** (include all indications):
  - Protocol number(s) and title(s)
  - Copies of protocol(s) and amendments
  - Blank CRFs
  - Copy of unsigned consent form
  - Names and addresses of monitoring organization(s) (e.g., CRO, sponsors monitoring team) in these pivotal studies
  - Description -of the primary efficacy endpoint(s) considered "critical" for the pivotal protocol study
  - List of study sites (domestic and/or foreign) for each pivotal study Preferably presented in a table, providing the following information for each study site:
    - name(s) of investigator(s)
    - addresses
    - number of subjects enrolled in each study arm
    - number of evaluable subjects
    - number of reportable AEs
    - number of SAEs including deaths
    - number of premature withdrawals
    - number of protocol violations
    - descriptive statistics of primary efficacy parameters (e.g., mean, SD, median, mean change from baseline, etc., or if the endpoint is non-parametric, number of deaths, number of responders, etc.)

Please send a copy of the cover letter, which lists all of the above data sent to DSI, to the application file.

Part II: **Site Specific Data**

1. Bart Barlogie, MD, PhD at theUniversity of Arkansas for Medical Sciences
2. Sundar Jagannath, MD at St. Vincent's Comprehensive Cancer Center, NY

For each study site listed above, please submit the following information:

- Address and phone number of the site
- Investigator's 1572
- List of investigator(s) and sub-investigators on 1572, and their c.v.
- Protocol and amendments approved for the site
- Sample blank CRF and case report data tabulations for the site with coding key
- Copies of completed CRFs of all (or selected number of subjects enrolled
- Randomization list for the site
- Total number of subjects entered in each study arm
- The number of drop outs/discontinued subjects, identified by the subjects' study numbers for the site, together with the reasons for each dropout/discontinuation
- List by the subject's study numbers all evaluable / inevaluable subjects
- List by the subject's study numbers all reportable AEs, SAEs and deaths with a narrative for all SAEs and deaths
- List of protocol violations and protocol deviations for the site
- Results (by site) of the "critical" primary efficacy parameters (with descriptive statistics: mean, SD, median, range at baseline and at endpoint, or change from baseline at endpoint, etc., or if the endpoint is non-parametric, number of deaths number of responders, etc.)
- Data listing of the efficacy endpoint data for \ ch subject for each of the centers
- IRB names (and SOPs)
- Names of monitors and monitoring logs

MESSAGE CONFIRMATION

01/31/03 16:52
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
01/31	01'08"	617 551 3742	CALLING	03	OK	0000

01/31/03 16:50 FDA-DODP → 916175513742 NO.013 P01

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To:	Tanya Lewis, M.S.	**From:**	Sean Bradley, CSO
Fax:	617-551-3742	**Fax:**	310-827-4590
Phone:	617-551-8951	**Phone:**	301-594-5770
Pages, including cover sheet:	3	**Date:**	January 31, 2003
Re:	NDA 21-602, VELCADE (1)		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

May 12, 2003

MILLENNIUM

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

NDA # 21-602 – VELCADE™ (bortezomib) for Injection
GENERAL CORRESPONDENCE
RE: PHASE 4 COMMITMENT LETTER

Dear Dr. Pazdur:

Attached is the sponsor's agreement to the phase 4 commitments proposed by the Agency. If you have any questions, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis

Tanya Lewis, MSc
Senior Manager
Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

MILLENNIUM

May 06, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Statistical Information, Amendment #030

Dear Dr. Pazdur:

Reference is made to an Information Request that was e-mailed by Dr. Bross on May 3, 2003. The response to your request is included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/30/2003 rev. 4 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Bernadette Bowen for /

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-044

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

May 6, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment #029

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Further reference is made to a fax received May 1, 2003 from Mr. Sean Bradley and a teleconference on May 2, 2003 between Millennium and FDA. This amendment to the NDA provides Millennium's response to the Agency's fax. A copy of the May 1st fax is attached for reference.

This electronic submission was scanned with Symantec antivirus software, Version 8.00.9374, virus definition file 4/30/2003 rev. 4 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody Brown
Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
Phone: 617-551-4977
Fax: 617-551-3742
M-043

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679-7000
mlnm.com

Facsimile Transmittal

MILLENNIUM

TO	Sean Bradley - FDA	FAX	(301) 827-4590	
FROM	Melody A. Brown	DATE	05-01-03	
RE	Request for USAN Document for bortezomib; NDA 21-602			
CC		PAGES	including cover sheet	
x Urgent	☐ For Review	☐ Please Comment	☐ Please Reply	☐ FYI

MESSAGE:

Sean,

In a phone conversation with Dr. Liang last night, he requested that I fax to you a copy of the acceptance letter from USAN for the name *"bortezomib"*. Please find a copy of this letter attached.

Let me know if you have any questions.

Regards,

Melody A. Brown
Director, Regulatory Affairs -- CMC
Millennium Pharmaceuticals
(617) 551-4977 phone
(617) 551-3742 fax

American Medical Association
515 North State Street
Chicago, Illinois 60610

Telefax: 312-464-4028
sophia_fuerst@ama-assn.org

SOPHIA V. FUERST, Director
312-464-4045

May 29, 2002

OO-13

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139

Attn: Melody Brown
Director, CMC Regulatory Affairs

Dear Ms. Brown:

It is my pleasure to inform you that the USAN Council adopted **bortezomib** as the United States Adopted Name for PS-341; LDP-341, a proteasome inhibitor intended for use in the treatment of multiple cancers, including multiple myeloma, chronic lymphocytic leukemia, non-Hodgkins lymphoma, and pancreatic, colon, lung, and prostate cancers.

Enclosed is a copy of the Statement of Adoption on **bortezomib**. Please review this information for accuracy, initial, and return the statement to me within 60 days of the date listed above. Irregardless, after 60 days, the information will be included in the *New in USAN* section of the USAN Website (www.ama-assn.org/go/usan), and be submitted to Mosby for publication in the journal of *Clinical Pharmacology and Therapeutics* and to the United States Pharmacopeial Convention, Inc., for publication in the *USP Dictionary of USAN and International Nonproprietary Names.*

Please note that this name has also been accepted by the WHO INN Expert Committee, and is scheduled for publication in pINN List 88.

Sincerely yours,

Sophia V. Fuerst

Sophia V. Fuerst
Secretary, USAN Council
Director, USAN Program

Enclosure: N02/31

May 29, 2002

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (OO-13)	BORTEZOMIB
PRONUNCIATION	bore tez' oh mib
THERAPEUTIC CLAIMS	treatment of multiple cancers, including multiple myeloma, chronic lymphocytic leukemia, non-Hodgkins lymphoma, and pancreatic, colon, lung, and prostate cancers (proteasome inhibitor)

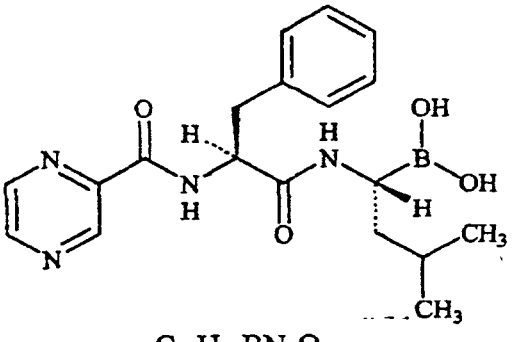
CHEMICAL NAMES

1) boronic acid, [(1*R*)-3-methyl-1-[[(2*S*)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]-

2) [(1*R*)-3-methyl-1-[[(2*S*)-3-phenyl-2-[(pyrazinylcarbonyl)amino]propanoyl]amino]butyl]boronic acid

3) *N*-[(1*S*)-1-benzyl-2-[[(1*R*)-1-(dihydroxyboranyl)-3-methylbutyl]amino]-2-oxoethyl]pyrazinecarboxamide

STRUCTURAL FORMULA



MOLECULAR FORMULA	$C_{19}H_{25}BN_4O_4$
MOLECULAR WEIGHT	384.24
TRADEMARK	Unknown as yet
MANUFACTURER	Millennium Pharmaceuticals, Inc.
CODE DESIGNATIONS	PS-341; LDP-341
CAS REGISTRY NUMBER	179324-69-7
WHO NUMBER	8331
SVF	

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

MILLENNIUM

May 01, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #028

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 30, 2003 from Mr. Sean Bradley. The response to your request is included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/30/2003 rev. 4 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Bernadette Bowen for T. Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-041

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

April 25, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #027

Dear Dr. Pazdur:

Reference is made to an Information Request that was e-mailed by Dr. Bross on April 23, 2003. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/23/2003 rev. 3 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Bernadette Bowen for

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-037

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.mlnm.com

April 24, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment #026

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Further reference is made to a fax received April 23, 2003 from Mr. Sean Bradley. A copy of the fax is attached following this letter. This amendment to the NDA provides Millennium's response to the Agency's questions.

This electronic submission was scanned with Symantec antivirus software, Version 8.00.9374, virus definition file 4/23/2003 rev. 3 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Colleen Costello, Ph. D.
Associate Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
Phone: 617-444-1602
Fax: 617-551-3742
M-036

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

MILLENNIUM

April 24, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #025

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 23, 2003 to Mr. Sean Bradley. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/23/2003 rev. 3 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Bernadette Bowen for

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-035

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

April 18, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #024

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 17, 2003 to Mr. Sean Bradley. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/16/2003 rev. 8 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Bernadette Bowen for/

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-032

April 17, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #023

Dear Dr. Pazdur:

Reference is made to an Information Request that was e-mailed on April 15, 2003 from Dr. Peter Bross. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/16/2003 rev. 8 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-031

Millennium Pharmaceuticals, Inc.
75 Sidney Street
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Tel 617 679 7000
www.millennium.com

April 16, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Biopharm Information, Amendment #022

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 16, 2003 from Mr. Sean Bradley. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/9/2003 rev. 7 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-030

Millennium Pharmaceuticals, Inc.
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April 16, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #021

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 9, 2003 from Mr. Sean Bradley. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/9/2003 rev. 7 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-029

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April 16, 2003

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment #020

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Further reference is made to a fax received April 7, 2003 and a second fax received April 11, 2003 from Mr. Sean Bradley. Copies of both faxes are attached following this letter. As stated in the April 11th fax, questions 2 and 12 have been revised from the original fax of April 7th. Also, questions 7, 18 and 19 have been eliminated. This amendment to the NDA provides Millennium's response to the Agency's questions.

This electronic submission was scanned with Symantec antivirus software, Version 8.00.9374, virus definition file 4/9/2003 rev. 7 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody Brown
Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
Phone: 617-551-4977
Fax: 617-551-3742
M-027

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MILLENNIUM

April 10, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Pharmacometrics Information Request
Amendment # 019

Dear Dr. Pazdur:

Reference is made to a teleconference between the sponsor and the Agency, during which the Agency requested that the sponsor explain how to find patient treatment variables for study M34100-024. In response to your request, please note the following:

- An analysis dataset called ——— contains each patient's actual treatment group in a variable called ———
- The variable ——— contains the same information as ———, i.e., the dose level actually received. It was incorrectly stated during the teleconference that ——— in ——— indicates the scheduled treatment the patient was to receive.
- With the exception of two patients, the scheduled treatment is available in dataset R341024 and is also available in listing 16.2.4.1B. More information regarding these two exceptions can be found in Section 5.3.5.2.4, clinical study report, M34100-024, page 90.
- Patient identifying information in ——— which contains the randomization list, has dummy values for ———, ——— and ———. To find the true values for these, this dataset can be merged with dataset ——— by using the randomization number. The variable containing the randomization number is called ——— in ——— and ——— in ———
- Please refer to Section 5.3.5.2.4, clinical Study report, M34100-024, page 97 for additional randomization details.

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April 10, 2003

MILLENNIUM

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information Requests
Amendment # 018

Dear Dr. Pazdur:

Reference is made to Information Requests that were faxed on March 26, 2003 and April 3, 2003 from Mr. Sean Bradley requesting copies of bone marrow aspiration and biopsy reports for all CR[Blade] patients. In addition, the Agency requested bone marrow slides for the follow-up samples obtained from the following patients: 03-001, 06-002, 12-0027, and 14-0015. The sponsor has obtained and scanned local and central bone marrow reports for all CR[Blade] patients. The reports have been scanned into one pdf file and are bookmarked for ease of review.

The sponsor has also included the bone marrow slides for samples obtained from the following patients: 03-001, 06-002, 12-0027, and 14-0015. Each slide is coded with a number that was used for blinding purposes. The code and corresponding cycle and patient identifiers are noted on each protective case.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/9/2003 rev. 7 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure
M-025

Millennium Pharmaceuticals, Inc.
75 Sidney Street
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April 8, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment # 017

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Further reference is made to a fax received April 3, 2003 from Mr. Sean Bradley. This amendment to the NDA provides Millennium's response to question 3 on the April 3rd fax.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 4/2/2003 rev. 20 and is virus free

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody A. Brown
Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
Phone: 617-551-4977
Fax: 617-551-3742
M-023

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April 8, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
PK Information, Amendment #016

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 3, 2003 from Mr. Sean Bradley. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition 4/2/2003 rev. 20 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-022

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April 7, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #015

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 3, 2003 from Mr. Sean Bradley. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 4/2/2003 rev. 20 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-021

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MILLENNIUM

April 4, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #014

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 3, 2003 from Mr. Sean Bradley regarding our clinical studies. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 4/2/2003 rev. 20 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-020

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MILLENNIUM

April 4, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical and Regulatory Information, Amendment #013

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on April 1, 2003 from Mr. Sean Bradley that requested information regarding our clinical studies and the regulatory history of our submission. The responses to your questions are included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 4/2/2003 rev. 20 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

M-019

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MILLENNIUM

April 1, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Non-clinical Information, Amendment #012

Dear Dr. Pazdur:

Subsequent to the submission of NDA #21-602 for VELCADE (bortezomib) for Injection, a few minor errors have been identified in the interim report (3-month) and final report (6-month) of Study No. 57285: A 26-Week Intravenous Injection Toxicity Study of PS-341 in the Albino Rat and in Study No. 57284: A 38-Week (13-Cycle) Intravenous Injection Toxicity Study of PS-341 in the Cynomolgus Monkey. Three report amendments have been issued to address these errors and are submitted with this brief summary of the changes. The minor changes to the VELCADE submission documents resulting from these report amendments are detailed in full on the following pages. These changes do not have substantive impact on the overall interpretation of the nonclinical safety data as it relates to human safety.

Two of the three report amendments address minor typographical and/or entry errors in the toxicokinetic reports in both the interim report (3-month) and full report (6-month) for Study No. 57285: A 26-Week Intravenous Injection Toxicity Study of PS-341 in the Albino Rat. Supplemental data was also added to the pharmacodynamic report for the interim report (3-month) for Study No. 57285 to express proteasome inhibition data by both proteasome specific activity and the chymotryptic:tryptic activity ratio. This addition of data allows for better continuity of presentation of pharmacodynamic activity results for all the chronic toxicology studies of 3 months or greater duration. These changes and additions do not affect any of the information provided in the nonclinical summary or overview submission documents.

The third report amendment addresses changes to the $AUC_{(0\text{-}24hr)}$ values expressed for Weeks 37 and 38 in the toxicokinetic report for Study No. 57284: A 38-Week (13-Cycle) Intravenous Injection Toxicity Study of PS-341 in the Cynomolgus Monkey. In error, the

AUC data for these sampling intervals was expressed as $AUC_{(0\text{-}24hr)}$ when the data presented was for $AUC_{(0\text{-}72hr)}$.

Therefore, the actual $AUC_{(0\text{-}24hr)}$ values are lower than indicated in this report and the safety margins discussed in the nonclinical overview are similarly lower than originally written.

These changes affect the information presented in the pharmacokinetics summary, toxicology summary, nonclinical overview and tabulated summaries. The changes to each section are itemized on the following pages of this cover letter with the changes underlined where appropriate. In addition, the changes are highlighted in colored text in the revised documents.

The minor changes to the VELCADE submission documents contained herein do not have substantive impact on the overall interpretation of the nonclinical safety data as it relates to human safety.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 3/26/2003 rev 2 and is virus free.

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs

Enclosure

bb:TL

M-017

In addition to the full report amendments provided herein, the following changes need to be noted in the nonclinical CTD summary and overview documents:

1. Nonclinical Overview, Section 2.4.4.2.6, pg. 28, paragraph 4, sentence 3.

   From: This dosage was associated with mean $AUC_{(0\text{-}24)}$ and C_{max} values of 83.1 hr*ng/mL and 48.2 ng/mL and peak inhibition of 20S chymotryptic:tryptic ratio proteasome activity of 75% at Week 38.

   To: This dosage was associated with mean $AUC_{(0\text{-}24)}$ and C_{max} values of 45.4 hr*ng/mL and 48.2 ng/mL and peak inhibition of 20S chymotryptic:tryptic ratio proteasome activity of 75% at Week 38.

2. Nonclinical Overview, Section 2.4.4.12.2, pg 36, paragraph 5, sentence 3.

   From: In the 9-month IV toxicity study in the monkey, the MTD was the lowest dosage studied, 0.05 mg/kg (0.6 mg/m^2), and resulted in mean $AUC_{(0\text{-}24)}$ and C_{max} values of 83.1 hr*ng/mL and 48.2 ng/mL at Week 38.

   To: In the 9-month IV toxicity study in the monkey, the MTD was the lowest dosage studied, 0.05 mg/kg (0.6 mg/m^2), and resulted in mean $AUC_{(0\text{-}24)}$ and C_{max} values of 45.4 hr*ng/mL and 48.2 ng/mL at Week 38.

3. Nonclinical Overview, Section 2.4.4.12.2, pg. 36, paragraph 5, sentence 6.

   From: Therefore, on the basis of AUC, the safety margins are 2.5- and 1.5-fold at the MTDs in the rat and monkey, respectively, compared to the human clinical AUC.

   To: Therefore, on the basis of AUC, the safety margins are 2.5- and 0.8-fold at the MTDs in the rat and monkey, respectively, compared to the human clinical AUC.

4. Pharmacokinetics Summary, Section 2.6.4.3.1.2, pg. 7, paragraph 4, sentence 1.

   From: At Week 37 and Week 38, the C_{max} did not differ but the clearance was lower than the corresponding values observed on Week 5.

   To: At Week 37 and Week 38, the C_{max} did not differ but the clearance was lower than the corresponding values observed on Week 1.

5. Pharmacokinetics Summary, Section 2.6.4.3.1.2, pg. 7, paragraph 4, sentence 3.

   From: There was a 2- to 3-fold increase in the $t_{1/2}$ and a more than doubling of the AUC.

To: There was a 2- to 3-fold increase in the $t_{1/2}$ and almost a doubling of the AUC.

6. Pharmacokinetics Summary, Table 2.6.4-2, pg. 25, Week 37 AUC_{0-24} (ng/mL*hr) values.

   From: 66.9 ± 28.9, 108 ± 17.0, and 138 ± 46.7.

   To: 38.5 ± 5.56, 58.4 ± 13.8, and 72.8 ± 13.8, respectively.

7. Pharmacokinetics Summary, Table 2.6.4-2, pg. 25, Week 38 AUC_{0-24} (ng/mL*hr) values.

   From: 83.1 ± 38.1, 140 ± 29.5, and 170 ± 33.1.

   To: 45.4 ± 10.9, 74.9 ± 17.8, and 92.3 ± 14.3, respectively.

8. Toxicology Summary, Section 2.6.6.3.12, pg. 42, paragraph 4, sentences 6 and 7.

   From: The Week 37 and 38 $AUC_{(0-24)}$ values were either greater than or similar to the Week 5 values. The $AUC_{(0-24)}$ values at Week 37 were 66.9, 108.0, and 138 hr*ng/mL and, at Week 38, 83.1, 140.0, and 170.0 hr*ng/mL at 0.050, 0.075, and 0.100 mg/kg (0.6, 0.9, and 1.2 mg/m^2), respectively.

   To: The Week 37 and 38 $AUC_{(0-24)}$ values were similar to the Week 5 values. The $AUC_{(0-24)}$ values at Week 37 were 38.5, 58.4, and 72.8 hr*ng/mL and, at Week 38, 45.4, 74.9, and 92.3 hr*ng/mL at 0.050, 0.075, and 0.100 mg/kg (0.6, 0.9, and 1.2 mg/m^2), respectively.

9. Toxicology Summary, Section 2.6.6.3.12, pg. 43, paragraph 3, sentence 3.

   From: This dosage was associated with mean $AUC_{(0-24)}$ and C_{max} values of 83.1 hr*ng/mL and 48.2 ng/mL and peak inhibition of 20S chymotryptic:tryptic ratio proteasome activity of 75% at Week 38.

   To: This dosage was associated with mean $AUC_{(0-24)}$ and C_{max} values of 45.4 hr*ng/mL and 48.2 ng/mL and peak inhibition of 20S chymotryptic:tryptic ratio proteasome activity of 75% at Week 38.

10. Toxicology Summary, Section 2.6.6.9.2, pg. 77, paragraph 2, sentence 2.

    From: In the 9-month IV toxicity study in the monkey, the MTD was the lowest dosage studied, 0.05 mg/kg (0.6 mg/m^2), and resulted in mean $AUC_{(0-24)}$ and C_{max} values of 83.1 hr*ng/mL and 48.2 ng/mL at Week 38.

    To: In the 9-month IV toxicity study in the monkey, the MTD was the lowest dosage studied, 0.05 mg/kg (0.6 mg/m^2), and resulted in mean $AUC_{(0-24)}$ and C_{max} values of 45.4 hr*ng/mL and 48.2 ng/mL at Week 38.

11. Toxicology Summary, Section 2.6.6.9.2, pg. 77, paragraph 2, sentence 5.

    From: Therefore, on the basis of AUC, the safety margins are 2.5- and 1.5-fold at the MTDs in the rat and monkey, respectively, compared to the human clinical AUC.

    To: Therefore, on the basis of AUC, the safety margins are 2.5- and 0.8-fold at the MTDs in the rat and monkey, respectively, compared to the human clinical AUC.

12. Tabulated Summary, 2.6.5.4D, Pharmacokinetics: Pharmacokinetics After Multiple IV Doses (Week 37 of a 38-week Toxicity Study), PK parameters, $AUC_{0\text{-}24}$ (hr*ng/mL) values.

    From: 66.9 ± 28.9, 108 ± 17.0, and 138 ± 46.7.

    To: 38.5 ± 5.56, 58.4 ± 13.8, and 72.8 ± 13.8, respectively.

13. Tabulated Summary, 2.6.5.4D, Pharmacokinetics: Pharmacokinetics After Multiple IV Doses (Week 37 of a 38-week Toxicity Study), PK parameters, $AUC_{0\text{-}24}$/dose (hr*ng/mL/mg*kg) values.

    From: 1340 ± 577, 1450 ± 226, and 1380 ± 466

    To: 770 ± 111, 778 ± 180, and 728 ± 138, respectively

14. Tabulated Summary, 2.6.5.4E, Pharmacokinetics: Pharmacokinetics After Multiple IV Doses (Week 38 of a 38-week Toxicity Study), PK parameters, $AUC_{0\text{-}24}$ (hr*ng/mL) values.

    From: 83.1 ± 38.1, 140 ± 29.5, and 170 ± 33.1.

    To: 45.4 ± 10.9, 74.9 ± 17.8, and 92.3 ± 14.3, respectively.

15. Tabulated Summary, 2.6.5.4E, Pharmacokinetics: Pharmacokinetics After Multiple IV Doses (Week 38 of a 39-week Toxicity Study), PK parameters, $AUC_{0\text{-}24}$/dose (hr*ng/mL/mg*kg) values.

    From: 1660 ± 761, 1870 ± 390, and 1700 ± 331.

    To: 909 ± 218, 999 ± 237, and 922 ± 143, respectively.

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MILLENNIUM

March 31, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
PK and Clinical Information, Amendment #011

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on March 26, 2003 from Mr. Sean Bradley that requested information from our PK and clinical studies. The responses to your questions are included in this submission.

This electronic submission was scanned with Symatec Antivirus software, Version 8.00.9374, virus definition file 3/26/2003 rev 2 and is virus free.

If you have any questions regarding this submission, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs

Enclosure

bb:TL

M-016

Millennium Pharmaceuticals, Inc
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March 27, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Clinical Information, Amendment #010

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on March 24, 2003 from Mr. Sean Bradley that requested information from our clinical studies. The response to your questions is included in this submission.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 3/26/2003 rev 2 and is virus free.

If you have any questions regarding this submission, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs &
Pharmacovigilance Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

Tracking number M-015

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MILLENNIUM

March 26, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
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1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Information Amendment, Number 009

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on March 17, 2003 from Mr. Sean Bradley that requested information from our nonclinical pharmacology studies. The information is included in this submission.

If you have any questions regarding this submission, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Sr. Mgr., Worldwide Regulatory Affairs &
Pharmacovigilance Millennium Pharmaceuticals, Inc.

Enclosure

bb:TL

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MILLENNIUM

March 26, 2003

Robert Kane, M.D.
Medical Officer
Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: VELCADE™ (bortezomib) for Injection
NDA # 21-602
Amendment #008
Clinical Safety Information

Dear Dr. Kane:

In response to our telephone conversation on Friday, March 21, 2003, I have attached a table that was created to assist in your evaluation of the dose toxicity relationship in study M34100-024. This information is the same information in fax submitted on March 25, 2003.

If you have any questions or comments, please contact me at (617) 551-8951.

Sincerely,

Tanya Lewis

Tanya Lewis, MS
Sr. Mgr., Regulatory Affairs
(tel) (617) 551-8951
(fax) (617) 551-3742

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March 24, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment # 007

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Reference is also made to a teleconference held on February 26, 2003 between Millennium participants and FDA chemists. In the teleconference, Millennium explained the need to update the NDA with information about the QC testing of two lots of drug substance that are intended for use in commercial launch supplies. Further reference is made to a telephone message from Mr. Sean Bradley on March 20, 2003 in which FDA agreed to allow Millennium Pharmaceuticals to update the QC release testing information of the NDA to include Ash Stevens, Inc.

This amendment to the NDA provides an updated "Manufacturer" section for the drug substance indicating that two lots of drug substance intended for commercial launch supplies were QC tested by [redacted]

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 3/19/2003 rev. 2 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody A. Brown
Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
Phone: 617-551-4977
Fax: 617-551-3742
M-012

Millennium Pharmaceuticals, Inc.
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March 17, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment # 006

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # ——— Reference is also made to an IND amendment for PS-341, IND # ———, Serial # 222 where Millennium committed to provide FDA with an update to the stability report for the PS-341 drug substance submitted in the original submission of NDA # 21-602. This amendment to NDA 21-602 provides twelve month data on lot ———. In addition, we are providing three month data on lot ——— and lot ——— A brief summary of the results is also provided.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 2/26/2003 rev. 7 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody A. Brown
Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
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March 5, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment # 005

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Reference is also made to a teleconference held on February 26, 2003 between Millennium participants and FDA chemists. In the teleconference, Millennium committed to updating the NDA with information about the change in the vial washer used at [redacted] in the manufacture of Velcade for Injection.

This amendment to the NDA contains an update to the "Regional" section of Module 3 in the Master Batch Record for the drug product to include the details of the change made to the vial washer by [redacted]

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 2/26/2003 rev. 7 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody A. Brown
Director – CMC Regulatory Affairs
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February 27, 2003

MILLENNIUM

Richard Pazdur, Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: VELCADE™ (bortezomib) for Injection
NDA# 21-602
CMC Information Amendment # 004

Dear Dr. Pazdur:

Reference is made to our New Drug Application for VELCADE™ (bortezomib) for Injection, NDA # 21-602. Reference is also made to an IND amendment for PS-341, IND # [redacted], Serial # 222 and to a teleconference with FDA on February 26, 2003 where Millennium committed to provide FDA with an update to the stability report for the VELCADE™ (bortezomib) for Injection product submitted in the original submission of NDA # 21-602. This amendment to NDA 21-602 provides eighteen month data on lot # D1-1-1 of drug product, sixteen month data on lot # D2-1-1 and twelve month data on lot D3-1-1. In addition, we are providing six month data on lots D7-1-1 and D8-1-1 and three month data on D9-1-1. A brief summary of the results is also provided.

This electronic submission was scanned with Symantec Antivirus software, Version 8.00.9374, virus definition file 2/26/2003 rev. 7 and is virus free.

An exact duplicate of this submission is being provided to the New England District Office pursuant to 21 CFR 314.50 (d)(i)(v).

Please feel free to contact me if you have any questions.

Sincerely,

Melody A. Brown
Director – CMC Regulatory Affairs
Millennium Pharmaceuticals, Inc.
Phone: 617-551-4977
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February 26, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

Re: VELCADE™ (bortezomib) for Injection
NDA# 21-602
Clinical Information Amendment #3
Serial Number: 003

Dear Dr. Pazdur:

Reference is made to an Information Request that was faxed on February 21, 2003 from Mr. Sean Bradley that requested information from our Clinical trials and eNDA database. This information is provided electronically. In addition, provided is a SAS dataset to use as a reference for determining the names of the variables that contain patient identifiers for all datasets submitted in the CRT section (Module 5, Section 5.3.7) of the eNDA submitted on January 21, 2003. This electronic submission was scanned with the Norton Anti-Virus Corporate Edition V 8.00.9374 and is virus free.

As we discussed in the Post-NDA meeting on February 24, 2003 our responses include where the information resides in the eNDA. If you have additional questions regarding this submission please feel free to contact Tanya Lewis, Senior Manager of Regulatory Affairs at 617-551-8951.

Sincerely,

Lynne Nibert

Lynne Nibert, BS, MA
Manager, Regulatory Affairs

Enclosed: 2 electronic files

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February 07, 2003

Khin Mating U, M.D.
Medical Officer
Division of Scientific Investigations (HFD-45)
7520 Standish Place, Room 125
Rockville, MD 20855

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Information Amendment
Serial Number: 002

Dear Dr. U:

In response to a fax received on Friday, January 31, 2003 from Mr. Sean Bradley enclosed please find information relating to the pivotal study for eNDA # 21-602. This eNDA was submitted for VELCADE™ (bortezomib) for Injection on January 21, 2003. The day 45 meeting is scheduled for March 5, 2003 and the action date is July 21, 2003. We have requested and expect priority review of the eNDA. VELCADE is a new molecular entity that belongs to a class of compounds known as proteasome inhibitors indicated for the treatment of relapsed and refractory multiple myeloma.

In support of the VELCADE eNDA, one pivotal study M34100-025 was submitted and will be the subject of this information amendment. This study was an open-label, non-randomized study, single arm study. Therefore, the request for randomizations lists and total number of study subjects in each study arm is not applicable to this application.

Please note that the eNDA was submitted in the CTD format there is not a Volume 1.1. As agreed to during our conversation on February 5, 2003, I have included the clinical summary of the CTD which discusses the clinical data in detail that was provided in the eNDA. In addition, we have provided a one paper copy for the office, one paper copy for the field and one CD-ROM will be submitted to the electronic document room.

If you have any questions regarding this submission or require additional information or copies, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S
Senior Manager, Regulatory Affairs
Millennium Pharmaceuticals, Inc.

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January 22, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

Re: **VELCADE™ (bortezomib) for Injection**
NDA# 21-602
Clinical and CMC Information Amendment # 001

Dear Dr. Pazdur:

Reference is made to a telephone conversation between me and Sean Bradley on January 21, 2002 during which Mr. Bradley indicated that Millennium Pharmaceuticals, Inc. needed to submit a statement regarding our intentions for a pediatric indication. In addition, Mr. Bradley indicated that we should also submit the paper copies for the CMC reviewer's desk copy as a part of this amendment. In response to Mr. Bradley's request included below is a statement regarding pursuit of a pediatric indication.

Millennium Pharmaceuticals, Inc. will not pursue a pediatric indication in relapsed and refractory multiple myeloma.

As indicated in our cover letter to the NDA submission (January 21, 2003) there were changes made to the CMC section of the submission (Modules 2 and 3) from what was submitted in the December 31, 2002 submission. This amendment to the NDA provides paper copies of each of the revised pages of the CMC section. Only the revised pages are being submitted to the NDA at this time. No other changes have been made to the CMC section. The changes were made to correct a calculation error in the batch analyses tables for the drug substance and product. These tables have been updated and a new version of the tables was submitted in the electronic submission sent on January 21, 2003. These changes also required that we update information in the "Justification of Specifications" sections for drug substance and drug product. Updated versions of these sections were also included in the electronic submission sent on January 21, 2003. Finally, as a result of the change in batch analyses, two Certificates of Analyses were updated. This required a change in the Methods Validation Package to include these new Certificates. The exact sections and pages affected by these CMC changes are listed below.

Module 2, Quality Overall Summary
2.3.S.4.4 Table 2 , Pages 29-31
2.3.S.4.5 Pages 36-41
2.3.P.5.4 Table 2 Pages 85-88
2.3.P.5.4 Pages 89-94

Module 3, Chemistry, Manufacturing and Controls Information
Drug Substance
3.2.S.4.4 Table 2, Pages 585-587
3.2.S.4.5 Pages 592-608

Drug Product
3.2.P.5.4 Table 2, Pages 383-386
3.2.P.5.6 Pages 388-408

Regional Methods Validation Package
C of A Lot # 020149 Pages 4-5
C of A Lot # D 9-1-1 Pages 6-7

An exact duplicate of this submission is being submitted to the New England District Office pursuant to21 CFR 314.50 (d) (1) (v).

If you have any questions regarding the CMC section of this submission, please contact Melody Brown, Director, CMC Regulatory Affairs at 617-551-4977 or via secure e-mail at mebrown@mpi.com. Please feel free to contact me for all non-CMC questions regarding this submission at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S.
Senior Manager, Worldwide Regulatory Affairs
Millennium, Pharmaceuticals, Inc.

1112 002

RECEIVED
JAN 2 1 2003
CDR/CDER

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MILLENNIUM

DUPLICATE

RR2-001

January 21, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RECEIVED
JAN 2 4 2003
HFD-150 / CDER

Re: **VELCADE™ (bortezomib) for Injection**
New NDA/NDA# 21-602
User Fee ID # 4489

Dear Dr. Pazdur:

Pursuant to 21 CFR 314.50, enclosed is an electronic NDA (eNDA) in CTD format (NDA # 21-602; User Fee ID# 4489), which is being submitted by Millennium Pharmaceuticals, Inc. for VELCADE™ (bortezomib) for Injection for the treatment of relapsed and refractory multiple myeloma. VELCADE was granted fast track designation for the treatment of relapsed and refractory multiple myeloma and pursuant to those regulations, we submitted the NDA on a rolling basis. As committed to on December 31st, 2002, the attached submission includes the finalized nonclinical section, Module 4 of the eCTD. The finalized nonclinical section includes the complete histopathology report from the 9 month monkey study. In addition, the summary and overview of the nonclinical data contained in Module 2 are updated based on the finalized histopathology report. The changes had no impact on proposed draft labeling.

Based upon fast track designation, we are requesting priority review status. Since the time of the December 31st submission, VELCADE was granted orphan drug designation. A copy of that letter is included in Module 1 for your reference. Millennium is also seeking accelerated approval (21 CFR 314.500, Subpart H) on the basis of data from one pivotal phase 2 study, M34100-025, a supportive phase 2 study M34100-024 and three phase 1 studies. Response rate, a surrogate marker likely to predict clinical benefit, was analyzed in each of these studies. To demonstrate that response rate is an appropriate surrogate for survival, details are provided in module 2 of this submission regarding the relationship between response rate and survival. Also pursuant to Subpart H of the regulations, Millennium is conducting a confirmatory phase 3 study, M34101-039 and is committed to ensuring its timely completion as a condition of accelerated approval. The design of this study was agreed to with FDA prior to the start of the study as a "Special Protocol Assessment."

There were minor changes made to the document which provide greater functionality to the navigational aspects of the submission. In every module, there is access to modules 1 and 2 which contain the overall table of contents and the administrative and summary documents, respectively. Please see the instructional guide provided in Module 1 for additional details regarding the navigation of this submission. Originally, the clinical datasets were provided on a separate CD-ROM that needed to be uploaded independent of the DLT tape. In this new submission, we have provided the datasets on the DLT tape.

There are also changes that have been made to the CMC section of the submission (Modules 2 and 3). The batch analyses tables for the drug substance and drug product have been updated as a result of a calculation error made in the original submission. There are no changes to the specifications previously submitted as a result of these revised calculations. The justifications for drug substance and drug product specifications sections have also been updated. Finally, as a result of the change in data in the batch analyses tables, two certificates of analyses were also updated. The exact sections and pages affected by these CMC changes are listed below.

Module 2, Quality Overall Summary
2.3.S.4.4 Table 2 and Table 3 Pages 29-35
2.3.S.4.5 Pages 36-41
2.3.P.5.4 Table 2 Pages 85-88
2.3.P.5.4 Pages 89-94

Module 3, Chemistry, Manufacturing and Controls Information
Drug Substance
3.2.S.4.4 Table 2 and Table 3 Pages 585-591
3.2.S.4.5 Pages 592-609

Drug Product
3.2.P.5.4 Table 2 pages 383-386
3.2.P.5.4 Pages 388-408

Regional Methods Validation Package
C of A Lot # 020149 Pages 4-5
C of A Lot # D 9-1-1 Pages 6-7

Due to the changes described above we request that the Agency replace the previously uploaded version of this NDA with this new version, so that the Agency will have access to the most current information.

As mentioned previously, this is an electronic submission. All documents are provided in Adobe Portable Document format (PDF) file format (version 4). In addition, the annotated draft package insert (hypertext linked) is provided in both PDF and MS Word file formats. This submission is provided on a DLT tape (40/80 format) and has been virus scanned using Symantec Antivirus software, version 8.0 by Symantec Corporation and is virus free.

If you have any questions regarding the CMC section of this submission, please contact Melody Brown, Director, CMC Regulatory Affairs at 617-551-4977 or via secure e-mail at mebrown@mpi.com. Please feel free to contact me for all non-CMC questions regarding this submission at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S.
Senior Manager, Worldwide Regulatory Affairs
Millennium, Pharmaceuticals, Inc.

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MILLENNIUM

December 31, 2002

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

Re: **VELCADE™ (bortezomib) for Injection**
New NDA/NDA# 21-602
User Fee ID 3 4489

Dear Dr. Pazdur:

Pursuant to 21 CFR 314.50, enclosed is an electronic NDA (eNDA) in CTD format (NDA # 21-602; User Fee ID# 4489), which is being submitted by Millennium Pharmaceuticals for VELCADE™ (bortezomib) for Injection for the treatment of relapsed and refractory multiple myeloma. Another electronic copy is included for archival purposes. VELCADE was granted fast designation for the treatment of relapsed and refractory multiple myeloma and pursuant to those regulations, we plan to submit the NDA on a rolling basis. We are requesting priority review status. The attached submission contains finalized clinical and CMC sections and a draft nonclinical section. The finalized nonclinical section inclusive of the histopathology data from the 9 month monkey study will be submitted by January 24, 2003.

Pursuant to 21 CFR 314.500, Subpart H, Millennium is also seeking accelerated approval (21 CFR 314.500, Subpart H) on the basis of data from one pivotal phase 2 study, M34100-025, a supportive phase 2 study M34100-024 and three phase 1 studies. Response rate, a surrogate marker likely to predict clinical benefit was analyzed in each of these studies. To demonstrate that response rate is an appropriate surrogate for survival, details are provided in module 2 of this submission regarding the relationship between response rate and survival. Also pursuant to Subpart H of the regulations, Millennium is conducting a confirmatory phase 3 study, M34101-039 and is committed to ensuring its timely completion as a condition of accelerated approval. The design of this study was agreed to with FDA prior to the start of the study as a "Special Protocol Assessment."

As mentioned previously, this is an electronic submission. All documents are provided in Adobe Portable Document format (PDF) file format (version 4). In addition, the

annotated draft package insert (hypertext linked) will be provided in both PDF and MS Word file formats. This submission is provided on a DLT tape (40/80 format) and has been virus scanned using Symantec Antivirus software, version 8.0 by Symantec Corporation and is virus free. In addition, datasets in support of the clinical studies contained in this submission are provided on a CD-ROM which was scanned with Norton Anti-Virus Corporate Edition V 8.00.9374 Virus Definition: 12/24/2002 rev. 5 and is virus free.

To facilitate Agency review of this NDA, a NDA mapping document is included in module1. This document provides a cross-reference between the CTD and NDA maps.

A spirit of collaboration marks the path to this submission. The Agency was always willing to discuss and offer input on issues that arose during development. Of special note are the efforts of Mr. Sean Bradley who has worked diligently throughout this process to aid the sponsor in gaining critical feedback from the review team.

We look forward to a continued collaboration with the Agency and meeting with you at the post-NDA submission meeting. If you have any questions regarding the CMC section of this submission, please contact Melody Brown, Director, CMC Regulatory Affairs at 617-551-4977 or via secure e-mail at mebrown@mpi.com. Please feel free to contact me for all non-CMC questions regarding this submission at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis

Tanya Lewis, M.S.
Senior Manager, Worldwide Regulatory Affairs
Millennium, Pharmaceuticals, Inc.